Section II (Remarks)

By the present amendment, Claims 1-8, 10, 16-17 and 24-26 are pending and rejected, and Claims 9, 12-14 and 18-23 have been cancelled. Claim 10 has been amended to remove the dependency from now-cancelled Claim 9.

Claim 8 is an independent claim directed to a process for purifying 17α-acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione (VA-2914). The process involves first forming a VA-2914 isopropanol hemisolvate by dissolving VA-2914 in isopropanol under heat. The resulting solution is cooled to obtain crystalline VA-2914 isopropanol hemisolvate. The crystalline VA-2914 isopropanol hemisolvate is then isolated from the mother liquor, which separates the isopropanol hemisolvate from impurities that are soluble in isopropanol. Claims 1-7 depend, directly or indirectly, from Claim 8.

Claim 1 (which depends from Claim 8) specifies that the VA-2914 isopropanol hemisolvate crystals are formed by crystallizing VA-2914 in isopropanol, and adds the further steps of separating the VA-2914 isopropanol hemisolvate crystals and converting VA-2914 isopropanol hemisolvate into VA-2914.

Claim 2 (which depends from Claim 1) specifies that the formation of VA-2914 isopropanol hemisolvate crystals involves dissolving VA-2914 in isopropanol under heat, and subsequently cooling the resulting solution, optionally under stirring.

Claim 3 (which depends from Claim 2) specifies that the VA-2914 and isopropanol mixture is heated at a temperature between 75ºC and the solvent reflux temperature until complete dissolution of VA-2914, and subsequently, the resulting solution of VA-2914 in isopropanol is allowed to cool at a temperature between 0ºC and 30ºC.

Claim 4 (which depends from Claim 1) specifies that the VA-2914 isopropanol hemisolvate crystals are separated by filtration.

Claim 5 (which depends from Claim 1) specifies that the conversion of VA-2914 isopropanol hemisolvate into VA-2914 is carried out by recrystallization in a solvent, and Claim 6 (which depends from Claim 5), specifies that the solvent is ethanol/water or ethyl ether.

Claim 7 (which depends from Claim 8) specifies the manner in which the VA-2914 compound is initially obtained. The compound is initially obtained by acid hydrolysis of compound 3,3-(1,2-ethanedioxy)-5α-hydroxy-11β-(4-N,N-dimethylaminophenyl)-17α-acetoxy-19-norpregna-9-ene-20-one [carbinol acetate].

Claims 16 and 17 (which both depend from Claim 1) specify that the VA-2914 is in the form of a white crystalline solid (Claim 16), and has a melting point of around 189°C (Claim 17).

Claim 10 as amended is an independent claim directed to a process for obtaining 17α-acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione (VA-2914) isopropanol hemisolvate. The process involves dissolving VA-2914 in isopropanol under heat, allowing the resulting solution to cool to a temperature between 0°C and 30°C, and isolating the resulting VA-2914 isopropanol hemisolvate.

Claim 24 is an independent claim directed to isolated VA-2914, in the form of white crystals.

Claim 25 is an independent claim directed to isolated VA-2914, in the form of crystals with a melting point of around 189°C.

Claim 26 is an independent claim directed to isolated VA-2914, in the form of white crystals with a melting point of around 189°C.

Applicants reserve the right to pursue any cancelled claims in a continuation or divisional application.

Applicants note that the previous rejection of Claims 1, 5, and 8 under 35 USC 102(b) over Kim et al. WO96/30390 ("Kim") was withdrawn. Applicants also note that the rejection of Claim 15 under 35 U.S.C. 103 (a) over Kim in view of PCT WO 99/45022 by Cook et al. ("Cook") was withdrawn in view of the previous cancellation of Claim 15.

Rejection of Claims 19-22 under 35 U.S.C. 112, Second Paragraph

Claims 19-22 were rejected under 35 U.S.C. 112, second paragraph. These claims have been cancelled, thus mooting the rejection.

Rejection of Claims 9, 13, 18, and 23 Under 35 USC 102(b) Over Kim et al.

Claims 9, 13, 18, and 23 were rejected under 35 USC 102(b) over Kim et al. WO96/30390 ("Kim"). These claims have been cancelled, thus mooting this ground of rejection.

Rejection of Claims 1-8, 10, 12-14, 16-17, 19-22 and 24-26 Under 35 U.S.C. 102(b) Over Kim in view of PCT WO 99/45022 by Cook et al.

Claims 1-8, 10, 12-14, 16-17, 19-22 and 24-26 were rejected under 35 U.S.C. 103 (a) over Kim in view of PCT WO 99/45022 by Cook et al. ("Cook").

Claims 12-14 and 19-22 have been cancelled, thus mooting the rejection of these claims. The rejection of Claims 1-8, 10, 16-17, and 24-26 is respectfully traversed.

The Claimed Subject Matter

Claim 8 is an independent claim, and is directed to a process for purifying 17α-acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione (VA-2914). The process involves first forming VA-2914 isopropanol hemisolvate by dissolving VA-2914 in isopropanol under heat. The resulting solution is cooled to obtain crystalline VA-2914 isopropanol hemisolvate. Importantly, the crystalline VA-2914 isopropanol hemisolvate is then isolated from the mother liquor. Claims 1-7 and 16-17 depend, directly or indirectly, from Claim 8.

Claim 10 as amended is an independent claim directed to a process for obtaining 17α-acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione (VA-2914) isopropanol hemisolvate. The process involves dissolving VA-2914 in isopropanol under heat, allowing the resulting solution to cool to a temperature between 0ºC and 30ºC, and isolating the resulting VA-2914 isopropanol hemisolvate.

Claim 24 is an independent claim directed to isolated VA-2914, in the form of white crystals. Support for Claim 24 is essentially the same as that of Claim 23, with support for the white color of the crystals found in the specification on page 2, lines 1-4.

Claim 25 is an independent claim directed to isolated VA-2914, in the form of crystals with a melting point of around 189°C.

Claim 26 is an independent claim directed to isolated VA-2914, in the form of white crystals with a melting point of around 189°C.

Kim

Kim teaches purifying raw VA-2914 by a dissolution-evaporation stage in isopropanol, followed by a dissolution-evaporation stage in ethyl acetate and a final recrystallization stage from ether (example 7, lines 26-36).

With respect to Claims 8 and 10, Kim does not teach or suggest isolating an isopropanol solvate from a mother liquor, as claimed. Thus, any impurities that would be soluble in the mother liquor are reintroduced into the crystalline material when the isopropanol is removed by evaporation, except for impurities that are volatile enough to be removed be evaporation as the isopropanol is evaporated.

With respect to Claims 24-26, Kim does not teach obtaining isolated VA-2914 in the form of white crystals (Claim 24), isolated VA-2914 in the form of crystals with a melting point of around 189°C (Claim 25), or isolated VA-2914, in the form of white crystals with a melting point of around 189°C (Claim 26).

Cook

Cook et al. discloses compounds structurally related to VA-2914. The majority of the compounds disclosed in Cook were purified by chromatography. Example 4 discloses that a compound was recrystallized from ethanol, and Example 10 discloses that a compound was recrystallized from ether/hexane. Cook does not teach that any of the compounds were first converted to an isopropanol hemisolvate, and removed from the mother liquor, or converting a hemisolvate to the parent compound.

The Rejections Should be Withdrawn Since Neither Kim Nor Cook Teach All Elements of the Claims

As discussed in more detail below, the obviousness rejections should be withdrawn, because the references fail to teach each element of the claims.

The process of Claims 8 and 10 involve forming VA-2914 isopropanol hemisolvate by dissolving VA-2914 in isopropanol under heat, cooling the solution to obtain crystalline VA-2914 isopropanol hemisolvate, and isolating the crystalline VA-2914 isopropanol hemisolvate from the mother liquor. Neither Kim nor Cook teaches isolating a crystalline VA-2914 isopropanol hemisolvate from a mother liquor. This is an

important purification step, since impurities soluble in isopropanol are separated from the isopropanol hemisolvate precipitated from the isopropanol.

The process of Claim 1 (which depends from Claim 8) adds the further step of desolvating the hemisolvate. Neither Kim nor Cook expressly teach or suggest forming an isopropanol hemisolvate, so neither could expressly teach desolvating an isopropanol hemisolvate. Again, Kim teaches purifying raw VA-2914 by a dissolution-evaporation stage in isopropanol, followed by a dissolution-evaporation stage in ethyl acetate. Even if, arguendo, Kim formed an isopropanol hemisolvate in the first dissolution-evaporation stage, and desolvated the hemisolvate in the second dissolution-evaporation stage, such was clearly not appreciated. As with Claim 8, at a minimum, Kim does not teach or suggest removing an isopropanol hemisolvate from an isopropanol mother liquor. Claims 2-6 depend, directly or indirectly, from Claim 1, so the elements of these claims are similarly not disclosed by the combination of references.

The process of Claim 7 (which depends from Claim 8) specifies the manner in which the VA-2914 compound is initially obtained. The compound is initially obtained by acid hydrolysis of compound 3,3-(1,2-ethanedioxy)-5α-hydroxy-11β-(4-N,N-dimethylaminophenyl)-17α-acetoxy-19-norpregna-9-ene-20-one [carbinol acetate]. In contrast, Kim discloses the acid hydrolysis of a compound with a hydroxy group at the 17 position a 3,3-(1,2-ethanedioxy) protecting group, and a hydroxy group at a position beta to the ethanedioxy group. The hydrolysis of the 1,2-ethanedioxy group yields a 3,3-oxo group, and the hydroxy group at the beta position is eliminated (dehydrated) to yield a double bond at the 4-position (See page 5, conversion of Compound VII to Compound VIII).

Kim therefore does not teach or suggest hydrolyzing the 1,2-ethanedioxy group of an intermediate including the 17α-acetoxy group. Indeed, Compound VII is prepared from Compound VI, which includes a free hydroxy group and an epoxy group, by reaction with a Grignard reagent (Kim at page 13, lines 18-22). Excess Grignard reagent (roughly 5 equivalents) is used, as the hydroxy group is converted to a magnesium alkoxide (Page 13, lines 23-30).

It would not have been possible to perform Kim's purportedly improved synthesis with an acetoxy group present at the 17α-position, if such group were intended to remain on the molecule in subsequent steps (as required in pending Claim 7). As the Examiner

is no doubt aware, the reaction product of a Grignard reagent with an ester is a tertiary alcohol. If an acetoxy group were present at the 17α-position, it would have been cleaved by the excess Grignard reagent. Accordingly, it would be impossible to modify Kim to arrive at the process of Claim 7.

With respect to Claims 24-26, Kim does not teach or suggest obtaining isolated VA-2914 in the form of white crystals (Claim 24), isolated VA-2914 in the form of crystals with a melting point of around 189°C (Claim 25), or isolated VA-2914, in the form of white crystals with a melting point of around 189°C (Claim 26), and Cook does not overcome this deficiency. The melting point and color of the crystals is indicative of their relatively high purity. Kim expressly discloses forming a crystalline product with a yellow color and with a lower melting point, which makes it clear that Kim fails to teach or suggest forming VA-2914 of the same high purity as is claimed in Claims 24-26.

A combination of references cannot render a claimed process obvious if the combination does not teach each element of the claims. Since the combination of references does not teach all elements of these claims, the rejections should be withdrawn on this basis alone.

The Obviousness Rejections Should Be Withdrawn on the Basis of Superior Results

The Examiner has argued that the only difference between the claimed process and that taught by Kim et al. is in the solvent used for the desolvation and crystallization of the obtained VA-2914 isopropanol hemisolvate. Applicants respectfully disagree with this view. In both processes the solvent used for the desolvation and crystallization of the obtained VA-2914 isopropanol hemisolvate is diethyl ether (commonly referred to simply as ether). The method disclosed by Kim et al. comprises:

a) a dissolution-evaporation stage in isopropanol,

b) a dissolution-evaporation stage in ethyl acetate,

c) a recrystallization stage from ethyl ether.

On the other hand, the process of the instant invention comprises:

a) formation of an isopropanol hemisolvate and

b) separation of the isopropanol hemisolvate from the mother liquor (and any impurities that remain in the mother liquor)

Therefore, the process of the instant application differs from that of Kim et al. in the use of a recrystallization step from isopropanol and the removal of the crystalline material from the impurity-containing mother liquor, instead of a dissolution-evaporation step in isopropanol (which causes isopropanol-soluble impurities to be retained) followed by a dissolution-evaporation stage in ethyl acetate.

To demonstrate the unexpectedly superior purity obtainable using Applicants' claimed process over the process disclosed by Kim, Applicants have conducted a side-by-side comparison of both processes, starting from a similar raw sample of 87.5% purity. Following the process taught by Kim et al., the crude material (20.82 g) was dissolved in isopropanol (52 mL) and evaporated (three times) and then dissolved and evaporated in ethyl acetate (80 mL). The resulting residue was dissolved in ethyl ether (65 mL), set aside to crystallize, filtered and washed with ether (10 mL). This process afforded VA-2914 of 98.57% purity (m.p. = 183-185ºC). A second sample of the same crude material (20.82 g) was subjected to the process of the invention (examples 2 and 3 of the application), leading to VA-2914 with a purity of 99.20% (white crystals, m.p. = 189ºC). Purity was determined by HPLC analysis. A copy of the HPLC chromatograms of raw material (87.50% purity), VA-2914 purified by the process of Kim et al. (98.57% purity) and VA-2914 purified by the process of the invention (99.20% purity) are enclosed (Annex 1).

Thus, the claimed processes provide an improved process for purifying VA-2914. The problem has been solved by the claimed invention as demonstrated with the side-by-side comparison experiments, which show that the process of the invention allows the preparation of VA-2914 of significantly improved purity when compared with the process disclosed by Kim et al.

In this regard, it is important to highlight that the purity of an active pharmaceutical ingredient is clearly a necessary condition for commercialization. Impurities produced during manufacturing processes must be limited to very small amounts to meet established quality standards. Indeed, purities higher than 99% are routinely requested for active pharmaceutical ingredients. As a consequence, the purity

improvement achieved by the invention is essential in order to be able to commercialize VA-2914 as an active pharmaceutical ingredient.

As the Examiner is no doubt aware, when a crystalline material is provided in higher purity, it has a higher melting point. When a crystalline material is provided in lighter color, it has a higher purity. Thus, with respect to the subject matter of Claims 24-26, it is clear that the higher melting point and white color are indicative of higher purity.

Therefore, the question to determine is whether there is any teaching in Kim et al. that would have prompted the skilled person, faced with the problem of providing an improved process for purifying VA-2914, to perform the modifications required to arrive at the process of the present invention, i.e. to replace the dissolution-evaporation in isopropanol followed by dissolution-evaporation in ethyl acetate by recrystallization from isopropanol with expectations of arriving at the desired product with an improved purity.

A person skilled in the art, faced with the problem of providing an improved process for purifying VA-2914 and starting from Kim et al., could have chosen to modify the process taught by Kim et al. by several strategies: such as changing the solvent in the first dissolution-evaporation step in Kim et al., or in the second dissolution-evaporation step or in the recrystallization stage, or he could have chosen to replace any of the three above-mentioned steps in Kim et al. by a different purification technique such as extraction, sublimation, crystallization or chromatography.

However, the question is not whether the skilled person *could* have chosen to perform a first recrystallization from isopropanol, instead of a dissolution-evaporation in isopropanol followed by dissolution-evaporation in ethyl acetate, to arrive at an alternative purification process. The question is whether he *would* have chosen this option among all the existing alternatives, in the hope of arriving at an improved purification process because something in the prior art incited him to do so.

In this regard, document by Kim et al. does not contain any teaching that would have incited the skilled person to perform that modification in the hope of arriving at an improved purification route. Indeed, it discloses on page 15, lines 19-23, that:

> *"the compound of formula I can be purified by crystallization from ether in high yield and high purity (m.p.: 183-185°C)".*

Therefore, Kim et al. do not even mention or suggest that the use of isopropanol could have any effect on the final purity of VA-2914.

On the contrary, the inventors have surprisingly found that VA-2914 isopropanol hemisolvate presents very special solubility properties (lower solubility) that make it a very useful intermediate in the process of purification of VA-2914 when obtained by recrystallization. As a consequence, the whole process affords VA-2914 with an improved purity. However, if this hemisolvate is not prepared by recrystallization, the process does not benefit from the unexpected solubility properties of the hemisolvate, since no separation of said compound from the mother liquor containing all the soluble impurities is performed.

As mentioned before, Kim does not teach or suggest that the use of isopropanol could have any beneficial effect on the purification of VA-2914. It does not mention either that the species formed upon treatment with isopropanol could have any particular properties that could allow one to improve the purity of the final VA-2914 if it were prepared by recrystallization.

Therefore, the skilled person, in searching for a new method to purify VA-2914, would have not found any teaching or suggest in Kim et al. to specifically choose a recrystallization stage from isopropanol to purify VA-2914, among all the existing alternatives. In addition, the process of the present invention affords VA-2914 of an improved purity, which also proves that the above-mentioned choice is not a mere alternative, but a non-obvious alternative. Thus, the skilled in the art in searching for an improved process to purify VA-2914 would have not found any guidance in the prior art on how to arrive at such improved process.

Moreover, the applicants point out that Kim et al. published a paper (Steroids 2000, 65, 395-400), copy enclosed (previously provided), where the results of their previous patent were described (see page 396, first paragraph, last sentence - reference [9] refers to the U.S. patent application whose priority is claimed by Kim et al.). In this paper, the synthesis and purification of VA-2914 (compound 8 of the publication) is described in point 2.7. In this case, the dissolution-evaporation stage of the raw material in isopropanol was removed and so the product was just purified by a dissolution-evaporation stage in ethyl acetate followed by recrystallization. However, a product with a similar melting point as in Kim et al. was obtained (m.p. = 183-185ºC), thus indicating

that the dissolution-evaporation step in isopropanol did not influence the purity of the final compound. This is in stark contrast to the instantly claimed process, in which the recrystallization step from isopropanol allows one to improve the purity of the final product.

It is important to note that in order to purify raw VA-2914, several crystallization solvents were tested by the inventors, such as ethyl acetate, ethyl alcohol, isopropyl ether, acetone/water. However, in all cases, yellow crystals of VA-2914 with relatively low purity were obtained. Subsequent recrystallizations from the same or different solvents did not allow them to improve the purity. Surprisingly, only the use of isopropanol as a first recrystallization solvent gave rise to the formation of an hemisolvate derivative with unexpected solubility properties, which allowed the development of a new process of purification of VA-2914 which afforded the desired compound in higher purity. In other words, the problem solved by the present invention is not achieved by the mere use of an additional recrystallization step in the purification process, but by the use of isopropanol in a first recrystallization, which confers advantageous solubility properties to the resulting product (i.e., the hemisolvate is insoluble in the solvent, whereas the various (colored) impurities remain in the mother liquor). As already discussed, the skilled person would not infer from Kim that the isopropanol hemisolvate could have any advantageous solubility properties and would therefore not find any guidance in the prior art on how to arrive at an improved purification process of VA-2914.

Cook et al. refer to compounds structurally related to VA-2914. However, Cook et al. do not teach using recrystallization of an isopropanol hemisolvate, with impurities remaining in the mother liquor, to purify the compounds. Therefore, the skilled person in view of this document, either alone or combined with Kim et al., would have never arrived at the process of the invention.

For any of the above reasons, Applicants respectfully request that the Examiner withdraw the rejections of Claims 1-8, 10, 16-17 and 24-26 under 35 U.S.C. 103 (a).

CONCLUSION

In light of the arguments presented above, it is requested that the rejection of the pending claims be withdrawn, and that the patentability of the pending claims likewise be

acknowledged. All of Applicants' pending claims are now patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing, and to responsively issue a Notice of Allowance. If any issues require further resolution, the examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same.

Respectfully submitted,

/david bradin/

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David S. Bradin
Reg. No. 37,783
Attorney for Applicant(s)

INTELLECTUAL PROPERTY/
TECHNOLOGY LAW
Phone: (919) 419-9350
Fax: (919) 419-9354
Attorney File No.: 4258-113

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